Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy for the Treatment of Pseudomyxoma Peritonei, Peritoneal Carcinomatosis of Gastrointestinal Origin, and Peritoneal Mesothelioma

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage cytoreductive surgery and perioperative intraperitoneal chemotherapy when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Cytoreductive surgery and perioperative intraperitoneal chemotherapy for the treatment of pseudomyxoma peritonei may be considered medically necessary.

Cytoreductive surgery and perioperative intraperitoneal chemotherapy for the treatment of diffuse malignant peritoneal mesothelioma may be considered medically necessary.

When Policy Topic is not covered
Cytoreductive surgery and perioperative intraperitoneal chemotherapy is considered investigational for peritoneal carcinomatosis from colorectal cancer.

Considerations
The coding for this overall procedure would likely involve codes for the surgery, the intraperitoneal chemotherapy, and the hyperthermia.

Cytoreduction
There is no specific CPT code for the surgical component of this complex procedure. It is likely that a series of CPT codes would be used describing exploratory laparotomies of various components of the abdominal cavity, in addition to specific codes for resection of visceral organs, depending on the extent of the carcinomatosis.

Intraperitoneal Chemotherapy
CPT code 96446 identifies “chemotherapy administration into the peritoneal cavity via indwelling port or catheter.” When performed using a temporary catheter or performed intraoperatively, the unlisted code 96549 (unlisted chemotherapy procedure) would be reported.

Hyperthermia
CPT code 77605 identifies, “Hyperthermia, externally generated; deep.”

Description of Procedure or Service
Peritoneal carcinomatosis from non-ovarian malignancies has long been regarded as a terminal disease with limited survival. In an attempt to prolong survival, aggressive locoregional therapy, such as combining cytoreductive surgery with perioperative intraperitoneal chemotherapy, has been used.

**Background**

Pseudomyxoma peritonei is a clinicopathologic entity characterized by the production of mucinous ascites and mostly originates from epithelial neoplasms of the appendix. As the tumor grows, the narrow lumen of the appendix becomes obstructed and subsequently leads to appendiceal perforation. The neoplastic cells progressively colonize the peritoneal cavity and copious mucin production builds up in the peritoneal cavity. Appendix tumors causing pseudomyxoma peritonei range from a benign pathologic appearance (disseminated peritoneal adenomucinosis) to malignant pathologic findings (peritoneal mucinous carcinomatosis), with some intermediate pathologic grades. Clinically, this syndrome ranges from early pseudomyxoma peritonei, fortuitously discovered on imaging or during a laparotomy performed for another reason, to advanced cases with a distended abdomen, bowel obstruction, and starvation. The conventional treatment of pseudomyxoma peritonei is surgical debulking repeated as necessary to alleviate pressure effects. However, repeated debulking surgeries become ever more difficult due to progressively thickened intra-abdominal adhesions, and this treatment is palliative, leaving visible or occult disease in the peritoneal cavity. (1)

Peritoneal dissemination develops in approximately 10–15% of patients with colon cancer, and despite the use of increasingly effective regimens of chemotherapy and biologic agents in the treatment of advanced disease, peritoneal metastases are associated with a median survival of 6 to 7 months.

**Mesothelioma**

Malignant mesothelioma is a relatively uncommon malignancy that may arise from the mesothelial cells lining the pleura, peritoneum, pericardium, and tunica vaginalis testis. In the U.S., 200-400 new cases of diffuse malignant peritoneal mesothelioma (DMPM) are registered every year, accounting for 10-30% of all-type mesothelioma. (2) DMPM has traditionally been considered as a rapidly lethal malignancy with limited and ineffective therapeutic options. (2) The disease is usually diagnosed at an advanced stage and is characterized by multiple variably sized nodules throughout the abdominal cavity. As the disease progresses, the nodules become confluent to form plaques, masses, or uniformly cover peritoneal surfaces. In most patients, death eventually occurs as a result of locoregional progression within the abdominal cavity. In historical case series, treatment by palliative surgery, systemic/intraperitoneal chemotherapy, and abdominal irradiation results in a median survival of approximately 12 months. (2)

Surgical cytoreduction in conjunction with hyperthermic intraperitoneal chemotherapy is designed to remove visible tumor deposits with intraperitoneal chemotherapy to address remaining microscopic disease. By delivering chemotherapy intraperitoneally, drug exposure to the peritoneal surface is increased some 20-fold compared to systemic exposure. In addition, prior animal and in vitro studies have suggested that the cytotoxicity of mitomycin C is enhanced at temperatures greater than 39 degrees Celsius.

Cytoreductive surgery (CRS) consists of peritonectomy procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination. (3) The surgical procedure may be followed intraoperatively by the infusion of hyperthermic chemotherapy, most commonly mitomycin C. Inflow and outflow catheters are placed in the abdominal cavity, along with temperature probes to monitor the temperature. The skin is then temporarily closed during the chemotherapy perfusion, which typically runs for 1 to 2 hours. This procedure is referred to as hyperthermic intraperitoneal chemotherapy (HIPEC). Other methods of intraperitoneal chemotherapy include early postoperative intraperitoneal chemotherapy (EPIC).

**Rationale**

This policy was created in 2005, with the most recent MEDLINE literature search performed through August 2013.
Pseudomyxoma Peritonei

In 2010, Glehen et al. published a retrospective, multicenter cohort study to evaluate toxicity and prognostic factors after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) and/or early postoperative intraperitoneal chemotherapy (EPIC). (4) Patients had diffuse peritoneal disease from malignancies of multiple different histologic origins. Exclusion criteria were perioperative chemotherapy performed more than 7 days after surgery and the presence of extra-abdominal metastases. The study included 1,290 patients from 25 institutions who underwent 1,344 procedures between 1989 and 2007. HIPEC was performed in 1,154 procedures. Postoperative mortality was 4.1%. The principal origin of peritoneal carcinomatosis was pseudomyxoma peritonei in 301 patients. Median overall survival (OS) for patients with pseudomyxoma peritonei was not reached. (Median OS for all patients was 34 months.)

Additional information about the subgroup of patients with pseudomyxoma peritonei was provided by Elias and colleagues. (5) CRS was achieved in 219 patients (73%), and HIPEC was performed in 255 (85%). The primary tumor site was the appendix in 91% of patients, the ovary in 7%, and unknown in 2%. Tumor histology was disseminated peritoneal adenomucinosis in 51%, peritoneal carcinomatosis with intermediate features in 27%, and peritoneal mucinous carcinomatosis in 22%. Postoperative mortality was 4% and morbidity, 40%. Mean follow-up was 88 months. The 1-, 3-, and 5-year OS rates were 89.4%, 84.8%, and 72.6%, respectively. The 10-year survival rate was 54.8%. Median survival had not yet been reached but will exceed 100 months. Disease-free survival (DFS) was 56% at 5 years, and median duration of DFS was 78 months. A multivariate analysis identified 5 prognostic factors: extent of peritoneal seeding (p=0.004), institution (p<0.001), pathologic grade (p=0.03), gender (p=0.02), and use of HIPEC (p=0.04). When only the 206 patients with complete CRS were considered, the extent of peritoneal seeding was the only significant prognostic factor (p=0.004).

Vaira and colleagues (2009) reported their experience managing pseudomyxoma peritonei with CRS and HIPEC in a single institution in 60 patients, 53 of whom had final follow-up data. (6) The postoperative morbidity rate was 45%; no postoperative deaths were observed. The primary tumor was appendiceal adenocarcinoma in 72% of patients and appendiceal adenoma in 28%. Approximately half of the patients with adenocarcinoma had received previous systemic chemotherapy. Five- and 10-year OS rates were 94% and 85%, respectively, and 5- and 10-year DFS rates were 80% and 70%, respectively. Significant differences in improved OS were observed in patients who experienced complete surgical cytoreduction (p<0.003) and in those with histologic type disseminated peritoneal adenomucinosis versus those with peritoneal mucinous carcinomatosis (p<0.014).

Chua and colleagues (2009) reported the long-term survival of 106 patients with pseudomyxoma peritonei treated between 1997 and 2008 with CRS and HIPEC and/or EPIC. (7) Sixty-nine percent of patients had complete cytoreduction. Eighty-three patients (78%) had HIPEC intraoperatively, 81 patients (76%) had EPIC postoperatively, and 67 patients (63%) had both HIPEC and EPIC. Seventy-three patients had disseminated peritoneal adenomucinosis, 11 had peritoneal mucinous carcinomatosis, and 22 had mixed tumors. Mortality rate was 3%, and severe morbidity rate was 49%. Median follow-up was 23 months (range: 0–140 months). Median OS was 104 months with a 5-year survival rate of 75%. Median PFS was 40 months with 1-, 3-, and 5-year progression-free survival (PFS) rates of 71%, 51%, and 38%, respectively. Factors influencing overall survival included histopathologic type of tumor (p=0.002), with best survival in patients with disseminated peritoneal adenomucinosis and worst survival in patients with peritoneal mucinous carcinomatosis. Factors influencing survival include histopathologic type of tumor, the use of both HIPEC and EPIC, completeness of cytoreduction, and severe morbidity.

In 2008, Elias and colleagues reported the results of 105 consecutive patients with pseudomyxoma peritonei treated between 1994 and 2006 with CRS and hyperthermic intraperitoneal chemotherapy. (1) The primary tumor was the appendix in 93 patients, ovary in 3, urachus in 1, pancreas in 1, and indeterminate in 7. Tumor histology was disseminated peritoneal adenomucinosis in 48% of patients, intermediate in 35% and peritoneal mucinous carcinomatosis in 17%. At the end of surgery, 72% of
patients had no visible residual peritoneal lesions. Postoperative mortality was 7.6% and morbidity, 67.6%. Median follow-up was 48 months, and 5-year OS and DFS were 80% (95% confidence interval [CI]: 68-88%) and 68% (95% CI: 55-79%), respectively. On multivariate analysis, two factors that had a negative influence on DFS were identified, serum carbohydrate antigen 19.9 (CA 19.9) level (a marker of biliopancreatic malignancy) greater than 300 units/mL and nondisseminated peritoneal adenomucinosis tumor histology.

In 2007, Yan and colleagues conducted a systematic review on the efficacy of CRS and intraperitoneal chemotherapy for all relevant studies from 1996 to 2006. (8) There were no randomized controlled trials (RCTs) or comparative studies. Ten studies were included (with a total of 863 patients); all were uncontrolled, observational studies. Two studies had relatively long-term follow-up of 48 and 52 months, and median follow-up in the remaining studies was less than 3 years (range: 19-35 months). Median survival across all studies ranged from 51 to 156 months. One-, 2-, 3-, and 5-year survival rates varied from 80–100%, 76–96%, 59–96%, and 52–96%, respectively. Overall mortality rates varied from 0-18% and morbidity from 33–56%.

Peritoneal Carcinomatosis From Colorectal Cancer

Reviews from 2009 and 2010 (3, 9, 10) summarized studies of colorectal peritoneal carcinomatosis treated with CRS and HIPEC, some of which are included in the section below. These included one RCT (discussed below) with a second publication after 8 years of follow-up, (11, 12) one comparative study, (13) and numerous observational studies. Across studies, median OS after CRS and HIPEC in patients with peritoneal dissemination from colon cancer ranged from 13 to 63 months (median: approximately 18 months). A 2008 study by Elias et al. (14) reported OS of 63 months, which may be explained by the use of more contemporary chemotherapeutic regimens in the treatment of advanced stage colon cancer compared to earlier studies in which previous standard therapy was used. (3) For comparison, published reports of outcomes after systemic treatment of metastatic colon cancer with polychemotherapy (with or without biologic agents) ranged from 14.8 months to 22.6 months (median: 19.2 months). (3)

The one RCT identified was a 2003 single institution study. (12) Verwaal and colleagues randomly assigned 105 patients with peritoneal carcinomatosis to standard treatment with systemic chemotherapy (fluorouracil and leucovorin) and palliative surgery, if necessary (i.e., treatment of bowel obstruction), or to a second arm consisting of aggressive CRS and HIPEC followed by standard systemic chemotherapy. Patients with other sites of metastases, i.e., lung or liver, were excluded. The cytoreductive procedure consisted of stripping the parietal peritoneum and resection of infiltrated viscera, if possible. Most often, resection of the gall bladder, parts of the stomach, and spleen were performed. The greater omentum was also routinely removed. At the completion of resection, the presence of residual tumor was assessed. Hyperthermic mitomycin C was then administered intraperitoneally for 90 minutes. In the cytoreduction group, the most important complications were small bowel leakage and abdominal sepsis, but 48 of 49 patients (98%) who received CRS and HIPEC suffered from severe or life-threatening complications, such as heart failure, arrhythmias, or renal failure. Eight patients (16%) died as the result of treatment at 30 days. The primary endpoint was OS, measured from the time of randomization to death from any cause. After a median follow-up of 21.6 months, 20 of 51 patients (39%) in the standard therapy group were still alive compared to 30 of 54 patients (55%) in the cytoreduction group (hazard ratio [HR] for death 0.55 [95% CI: 0.32-0.95]; p=0.032). Median OS in the control group was 12.6 months compared to 22.4 months in the cytoreduction group. Subgroup analysis revealed that OS was particularly poor among patients with either residual tumor measuring greater than 2.5 mm or in patients with tumor involvement in 6 or more regions in the abdomen. In these groups, median survival was approximately 5 months, compared to 29 months in patients with no residual tumor.

An editorial on this randomized trial commented that although this study showed that CRS and HIPEC with systemic chemotherapy nearly doubles survival compared to systemic chemotherapy alone, it did not show how much of this benefit is derived from the surgery and how much from the HIPEC, (15) and
in a letter to the editor, Markman points out that the reported survival benefit may be primarily related to the cytoreduction, with added chemotherapy only contributing to increased morbidity. (16) Finally, new targeted systemic treatment options have emerged for colon cancer, specifically cetuximab and bevacizumab, which offer additional palliative options for colon cancer; the chemotherapy used in the randomized trial is no longer considered standard.

Aside from methodologic issues, results of the trial present complicated risk benefit questions that are not adequately addressed. If the main rationale for CRS is to provide a curative option, data regarding disease recurrence would be important. However, it is unknown whether survivors in either group lived with or without disease. If the main rationale for the therapy is palliation in terms of prolonging life or relieving specific symptoms (e.g., related to ascites or bowel obstruction), it is important to determine the quality of life associated with the 10-month improvement in median survival. Quality-of-life data were not reported in this randomized trial; however, the high incidence of major complications, and the reported mean length of hospitalization (29 days) suggested that this aggressive surgical approach has a significant impact on quality of life. Quality of life was addressed in 2001 in a case series of 64 patients undergoing CRS and intraperitoneal chemotherapy for peritoneal carcinomatosis. (17) The Functional Assessment of Cancer Therapy-Colon (FACT-C), activities of daily living subscale of the Short Form-36, Brief Pain Inventory, and Center for Epidemiologic Studies—Depression (CES-D) scales comprised the quality-of-life instruments used. Forty-eight of 64 enrolled patients (75%) completed the assessment before and at a mean of 12 days after surgery; 16 patients (25%) did not complete the survey either due to death (n=11) or missed appointments. By 6 months’ follow-up, only 39 patients (61%) were available, either due to death or continuing dropout. Among the respondents, overall quality of life decreased significantly from baseline to postsurgery but improved to greater than baseline at 3 months. However, these data are difficult to interpret without a control group and owing to the large number of dropouts due to death.

The randomized trial (12) reported 8-year follow-up of all patients alive until 2007. (11) This update had a minimum follow-up of 6 years for all patients (median: 7.8 years; range: 6–9.6 years). During follow-up, 1 patient crossed over from the standard arm to the CRS/HIPEC arm after recurrent disease at 30 months after randomization. At the time of this long-term follow-up, in the standard arm, 4 patients were still alive, 2 with disease and 2 without disease, and in the HIPEC arm, 5 patients were still alive, 2 with disease and 3 without disease. Median disease-specific survival was 12.6 months in the standard arm and 22.2 months in the CRS/HIPEC arm (p=0.028). Median PFS was 7.7 months in the standard arm and 12.6 months in the CRS/HIPEC arm (p=0.02).

De Cuba and colleagues reported a 2013 systematic review and meta-analysis of studies of colorectal cancer patients with both peritoneal and liver metastases who received CRS and HIPEC plus curative resection. (18) In their review, the authors compared the results of studies in this population to those of patients without liver metastases who received modern systemic chemotherapy only (irinotecan, oxaliplatin, and a biologic) or CRS plus HIPEC or EPIC. Median overall survival ranged from 6 to 36 months in patients with liver metastases, from 10 to 24 months in patients (without liver metastases) who received systemic chemotherapy only, and from 19 to 63 months in patients (without liver metastases) who received CRS plus HIPEC or EPIC. Patients with liver metastases had a 24% greater risk of death than those without liver metastases who received CRS plus HIPEC or EPIC (pooled HR: 1.24 [95% CI: 0.96-1.60]; p=NS). The authors observed that comparisons across studies are impaired by lack of standardization of the HIPEC or EPIC procedure (exposure technique, drugs and doses used, duration of exposure, temperature and flow rates). In 2013, the American Society of Peritoneal Surface Malignancies, a consortium of cancer centers performing CRS with HIPEC, published recommendations for standardizing the delivery of HIPEC in colorectal cancer patients with peritoneal dissemination treated in the U.S. to further research in this area.(19)

In 2013, Tsilimparis and colleagues reported on quality of life in 90 consecutive patients at their institution who underwent CRS and HIPEC. (20) Primary tumors were colorectal (21%), ovarian (19%), pseudomyxoma peritonei (16%), appendiceal (16%), gastric (10%), and peritoneal mesothelioma (13%). Health-related quality of life was assessed using the German version of the European
Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire, which assesses function and symptoms. Each scale/item is scored from 0 to 100, with higher scores indicating higher response (either greater function or greater symptom severity). The proportion of patients who returned questionnaires was 59% at 1 month, 47% at 6 months, 36% at 1 year, 19% at 2 years, and 7% at 3 years. After initial decline in the postoperative period, only constipation improved significantly at 6 months (42 patients). Pain, nausea/vomiting, and dyspnea improved significantly in the 6 patients reporting at 3 years. Mean global health status (patient self-assessment) and emotional function scores returned to baseline in the 17 patients reporting at 2 years, and physical and social function returned to baseline at 3 years. Other symptoms (fatigue, pain, insomnia, anorexia, and diarrhea), functions (role and cognitive), and financial problems worsened from baseline during the follow-up period. The authors acknowledge that quality of life studies in this patient population are complicated by survivor bias, varied primary diagnoses and natural history of disease.

In 2013, Klaver and colleagues reported a case series of 18 patients in 3 centers who had peritoneal recurrence of colorectal (13 patients) or appendiceal (5 patients) carcinomatosis and received a second CRS with HIPEC (mitomycin; 14 patients) or EPIC (5-fluorouracil; 3 patients) or both (1 patient). (21) Median time to recurrence after the primary procedure was 14 months (range: 1–33). Mean peritoneal cancer index (PCI, a summary of both lesion size and distribution of peritoneal surface malignancy used to estimate the likelihood of complete cytoreduction; lower scores are better (22)) was 6.3 on a scale of 39. No patients died within 30 days after the second procedure. During median follow-up of 10 months, 14 patients (78%) experienced a subsequent recurrence, with a median time to recurrence of 4.5 months. One- and 2-year OS were 74% and 50%, respectively.

In the 2010 retrospective, multicenter cohort study described above, (4) the principal origin of peritoneal carcinomatosis was colorectal adenocarcinoma in 523 patients. Median OS for this group was 30 months. Independent prognostic indicators in multivariate analysis were institution, histologic origin of the tumor, completeness of CRS, extent of carcinomatosis, and lymph node involvement.

Elias and colleagues (2008) compared 48 patients in the French Multicentric Database with peritoneal carcinomatosis arising from colon cancer who received palliative systemic oxaliplatin or irinotecan-based chemotherapy to 48 patients who underwent additional CRS and HIPEC at a single institution. (14) Chemotherapeutic regimen and duration of systemic chemotherapy were comparable in both groups. Results showed a significant improvement of long-term survival after complete macroscopic cytoreduction followed by HIPEC compared to systemic treatment alone. Median OS was 23.9 months in the control group and 62.7 months in the HIPEC group (p<0.05). Five-year survival rates were 13% and 51%, respectively.

In 2008, van Leeuwen and colleagues reported on a Swedish series of 103 patients treated between 2003 and 2006. (23) This study explored factors associated with postoperative morbidity and survival. Postoperative mortality in this center was less than 1%, and postoperative morbidity was 56%. Tumor type and optimal cytoreduction influenced survival. In this uncontrolled series, 2-year OS was 72% and DFS was 34%.

In 2004, Glehen and colleagues reported on a retrospective case series involving 28 institutions and 506 patients. (24) The study population comprised patients with peritoneal carcinomatosis related to colorectal cancer who underwent CRS and HIPEC between 1987 and 2002. Patients with extra-abdominal metastases were excluded. A variety of HIPEC protocols was used; mitomycin C was the most common. Some patients also received EPIC, sometimes after a previous intraoperative infusion. In the early postoperative setting, fluorouracil was most commonly used. At a mean follow-up of 53 months, morbidity and mortality rates were 23% and 4%, respectively, with a median survival of 19.2 months. Twenty patients (4%) died postoperatively. Major complications occurred in 116 patients (23%); digestive fistula was the most common major complication, occurring in 8% of patients, and was the cause of death in 7 of the 20 patients who died. In subgroup analysis, completeness of resection was the most significant prognostic indicator: Patients with complete resection of macroscopic disease had a median survival of 32.4 months compared to 8 months in those for whom complete resection was
not possible. Overall recurrence rate was 73%, with peritoneal recurrences noted in 42% of patients. The authors concluded that these results echoed those reported in smaller case series.

**Peritoneal Mesothelioma**

For a 2011 systematic review, Baratti and colleagues searched the PubMed database from 1979-2010 for studies on the clinical management of diffuse malignant peritoneal mesothelioma (DMPM). (2) The review included 14 studies with a total of 427 patients, 289 of whom underwent CRS with HIPEC, 2 with EPIC, and 106 with both. Studies that included patients with well-differentiated or low-grade types of mesothelioma were excluded. All included studies were prospective, nonrandomized, uncontrolled case series. Mean patient age ranged from 49 to 56 years. All institutions used peritonectomy and multivisceral resection to remove visible disease. HIPEC protocols varied widely among institutions in terms of technique, drugs, carriers, timing and temperature. Operative mortality and morbidity were reported in 11 monoinstitutional series. Operative mortality ranged from 0% to 10.5%. Overall, death occurred in 11 of 373 assessable patients (3.1%). In one multi-institutional series, mortality was 2.2%. Morbidity (severe and life-threatening complications) varied from 20% to 41%. For patients who underwent CRS and HIPEC, median OS ranged from 29.5 to 92 months. Median OS was not reached in 3 series, but exceeded 100 months in one of these. One-, 2-, 3-, and 5-year overall survival rates varied from 43–88%, 43%–77%, 43%–70%, and 33%–68%, respectively. In 4 studies, median PFS ranged from 7.2 to 40 months.

The largest study in the systematic review was a 2009 international registry study, for which 401 patients (99%) had complete follow-up. (25) Of these patients, 92% received HIPEC. Reasons for not receiving HIPEC included EPIC being given instead, intraoperative hemodynamic instability, and unclear reason. Median and 1-, 3-, and 5-year survival rates were 53 months, 81%, 60%, and 47%, respectively.

The review acknowledged the possibility of patient selection bias as an explanation for the superior survival noted with aggressive treatment over more conventional treatment modalities, since patients with poor performance status are generally excluded from CRS and HIPEC. The authors conclude that, even in the absence of controlled data, the evidence suggests that the use of CRS and HIPEC in the treatment of DMPM should be the benchmark against which other treatments should be evaluated.

In the 2010 retrospective, multicenter cohort study described above, (4) the principal origin of tumor was peritoneal mesothelioma in 88 patients. Median survival for this group of patients was 41 months. Independent prognostic indicators in multivariate analysis were institution, origin of peritoneal carcinomatosis, completeness of CRS, extent of carcinomatosis, and lymph node involvement.

**Ongoing Clinical Trials**

Two randomized Phase III trials in patients with peritoneal carcinomatosis were identified and are outlined in the following paragraphs.

A Phase III randomized pilot study compares OS in patients with advanced limited peritoneal dissemination of colon adenocarcinoma randomized to standard systemic therapy with or without cytoreduction surgery and hyperthermic intraperitoneal mitomycin C. (NCT01167725) Secondary outcomes include PFS, quality of life, toxicity, survival according to patient's peritoneal surface tumor genotype, and burden of circulating tumor cells. Expected enrollment is 340, and estimated primary completion date is May 2014.

The randomized, multicentric, Phase III PRODIGE-7 trial compares CRS alone to CRS plus HIPEC in patients with peritoneal carcinomatosis. This trial has reportedly neared completion of accrual and preliminary results are awaited. (19) However, no record of this trial was found on online site ClinicalTrials.gov or in the European Union Clinical Trials register.
Summary

**Pseudomyxoma peritonei**

Several case studies and a systematic review on the use of CRS and HIPEC have been published. Although no randomized trials or comparative studies have been published, the data have shown consistent, long-term DFS and OS with the use of this technique, compared to historic controls. Therefore, CRS and HIPEC may be considered medically necessary for this indication.

**Peritoneal carcinomatosis from colorectal cancer**

Numerous studies with different levels of evidence support the safety and feasibility of CRS and HIPEC, and existing data suggest a possible improvement in long-term survival of select patients. However, prospective randomized trials are needed to compare best available systemic therapy with and without CRS and HIPEC to determine optimal regimens and the exact effects of each step, which are currently unknown; an ongoing Phase III trial (PRODIGE-7) addresses the question of how much survival benefit is derived from cytoreduction and how much from HIPEC, as patients will be randomly assigned to HIPEC or no HIPEC after CRS. Additionally, quality-of-life data do not provide a clear picture of patient benefit. Therefore, CRS and HIPEC are considered investigational for this indication.

**Peritoneal mesothelioma**

The conventional treatment of peritoneal mesothelioma (diffuse malignant type) has resulted in a median survival of approximately 12 months. Although data on the use of CRS and HIPEC consists of nonrandomized case series without control groups, these have shown a significant prolongation of survival ranging from 29.5 to 92 months. Therefore, CRS and HIPEC may be considered medically necessary for this indication.

**Practice Guidelines and Position Statements**

National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology for colon cancer (v.3.2013) and for rectal cancer (v. 4.2013) consider the treatment of disseminated carcinomatosis with CRS and HIPEC to be investigational and do not endorse such therapy outside of a clinical trial. (26, 27) NCCN guidelines that specifically address the treatment of appendiceal tumors, pseudomyxoma peritonei and peritoneal mesothelioma were not identified.

A 2012 practice parameter from the American Society of Colon and Rectal Surgeons states that the treatment of patients with peritoneal carcinomatosis may include surgical cytoreduction. The role of HIPEC remains “insufficiently defined.”(28)

In 2007, the Society of Surgical Oncology issued a consensus statement on CRS and HIPEC in the management of peritoneal surface malignancies of colonic origin. (29) Their recommendation is that patients with peritoneal carcinomatosis without distant disease, in whom complete cytoreduction is possible, undergo HIPEC before systemic therapy. As of August 2013, an updated consensus statement has not been published.

References


**Billing Coding/Physician Documentation Information**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>77605</td>
<td>Hyperthermia, externally generated; deep (ie, heating to depths greater than 4 cm)</td>
</tr>
<tr>
<td>96446</td>
<td>Chemotherapy administration into the peritoneal cavity via indwelling port or catheter</td>
</tr>
</tbody>
</table>

**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/1/11</td>
<td>New policy; may be considered medically necessary.</td>
</tr>
<tr>
<td>3/1/12</td>
<td>Title changed to include peritoneal mesothelioma. Policy statement added that cytoreductive surgery and perioperative intraperitoneal chemotherapy for the treatment of peritoneal mesothelioma may be considered medically necessary. Use of the term “hyperthermic” changed to “perioperative” in the title and policy statements to include early postoperative intraperitoneal chemotherapy. Use of the term “cytoreduction” changed to “cytoreductive surgery” to be more specific.</td>
</tr>
<tr>
<td>3/1/13</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>3/1/14</td>
<td>No policy statement changes.</td>
</tr>
</tbody>
</table>

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.